REMARKS

Reconsideration and allowance of the instant application are respectfully requested.

Claim status

Claims 10-17 are withdrawn from consideration. Claims 1, 4-5, 7-9, and 19 are pending. Claims 2-3, 6, 18 and 20 are cancelled.

§112 Rejection

Claims 1, 4-5, 7-9, and 18-20 stand rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant traverses.

Applicant has amended claim 1 by removing the word "prior" in order to clarify the language of the claim. In light of this amendment, Applicant requests that the §112 rejection be withdrawn and the claims allowed.

§103 Rejection

Claims 1, 4-5, 7-9, 19 and 20 stand rejected as being obvious over U.S. Patent No. 6,565,782 (hereinafter Wang). Applicant traverses.

Applicant has amended claim 1 by incorporating previous claims 18 and 20 into its description which now describes a semipermeable hollow-fibre membrane,

particularly for use in hemodialysis, hemodiafiltration and hemofiltration, comprising: a hydrophilic, water-wettable membrane being based on a hydrophobic first polymer selected from the group consisting of an aromatic sulfone polymer, a polycarbonate, polyimide, polyetherimide, polyetherketone, polyphenylene sulfide, or a copolymer or a modification of these polymers, or a mixture of these polymers; and a hydrophilic second polymer selected from the group consisting of polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohol, polyglycol monoester, polysorbate, carboxymethylcellulose, or a modification or copolymer of these polymers. Claim 1 goes on to describe the semipermeable hollow-fibre membrane as possessing an open-pored, integrally asymmetric structure across its wall with a porous separating layer of thickness 0.1 to 2 µm on its inner surface facing the lumen and an open-pored supporting layer adjoining the separating layer, characterized in that a polyelectrolyte with negative fixed charges is physically bound in the separating layer, characterized in that the supporting layer is essentially free from polyelectrolyte with negative fixed charges, and having an ultrafiltration rate in albumin solution in the range of 25 to 60 ml/(h·m^2·mmHg), wherein after drying, the hollow-fibre membrane has a minimum sieving coefficient for cytochrome c of 0.8 combined with a maximum sieving coefficient for albumin of 0.005, and whereby the hollow-fibre membrane in the dry state is free from pore-stabilizing additives in the membrane wall.

The Examiner acknowledges that Wang lacks the specific thickness of the separating layer and the ultrafiltration rate in albumin solution, minimum sieving coefficient of cytochrome c and maximum sieving coefficient of albumin. The Examiner

then makes a tremendous "leap of faith" by simply asserting that because the membranes described in Wang are made of the same material and are produced by a process which is similar (exactly how "similar" as defined in this instance is not known) as claimed in the instant application, the membranes of Wang inherently possess the same characteristics as the membranes according to the instant invention.

According to the MPEP 2141.03,

> The person of ordinary skill in the art is a hypothetical person who is presumed to have known the relevant art at the time of the invention. Factors that may be considered in determining the level of ordinary skill in the art may include: (A) "type of problems encountered in the art;" (B) "prior art solutions to those problems;" (C) "rapidity with which innovations are made;" (D) "sophistication of the technology; and" (E) "educational level of active workers in the field. In a given case, every factor may not be present, and one or more factors may predominate."*In re GPAC*, 57 F.3d 1573, 1579, 35 USPQ2d 1116, 1121 (Fed. Cir. 1995); *Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 962, 1 USPQ2d 1196, 1201 (Fed. Cir. 1986); *Environmental Designs, Ltd. V. Union Oil Co.*, 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983).

MPEP 2141.03 goes on to state that:

> "The importance of resolving the level of ordinary skill in the art lies in the necessity of maintaining objectivity in the obviousness inquiry." *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718, 21 USPQ2d 1053, 1057 (Fed. Cir. 1991). The examiner must ascertain what would have been obvious to one of ordinary skill in the art at the time the invention was made, and not to the inventor, a judge, a layman, those skilled in remote arts, or to geniuses in the art at hand. *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 218 USPQ 865 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

Applicant believes that this patent application is clearly not directed toward a person on the street, but instead to one of ordinary skill in the art who is presently in the art of membrane technology. With this in mind, one having skill in the art would have at least a basic knowledge of membrane technology and, with respect to the present patent

application, at least a basic knowledge in membrane technology for blood purification must be required. It is will all due respect that the Applicant must state that the Examiner's analysis is not demonstrating a well founded knowledge in membrane technology and more specifically it is not demonstrating knowledge in the treatment of blood by hemodialysis, hemodiafiltration and hemofiltration.

As stated in the previous office action, one having skill in the art would already know from the information provided that in order for a membrane to be useful for hemodialysis, hemodiafiltration and hemofiltration, the membrane must have a distinct separating pore size in order to perform as a membrane for blood purification. As is explained in the second paragraph of page 1 of the original specification, membranes for these applications are directed toward the removal of low molecular proteins such as β_2-microglobuulin (β_{2M}) along with the removal of large quantities of water and low-molecular uremic toxins. At the same time, proteins such as albumin must remain in the blood to be treated (i.e., the membrane must reject these proteins). From this information, one having ordinary skill in the art would know that such a membrane must not be a microfiltration membrane having a pore size in the separating layer of more than 0.1µm. Applicant explained this in great detail in our response to the previous office action.

Additionally, as stated previously by the Applicant, there is a recitation of the pore size in claim 1 of the instant application, contrary to the Examiner's allegation. For membranes like the ones described in claim 1 of the present invention, it is not possible

to actually measure the pore size in the separating layer by, for example, visual inspection of an SEM picture. One must rely upon indirect measures to determine the pore size. One such method of indirect measure is the determination of sieving coefficients for certain substances. If the sieving coefficient for a certain substance is zero, the pore size of the membrane is such that this substance is completely or nearly completely retained by the membrane (i.e., the membrane is dense with respect to this substance). If the sieving coefficient for another substance is 1 or nearly 1, the pore size of the membrane is such that this substance can completely or nearly completely pass through the membrane.

Thus, for membranes such as those described in claim 1 of the present invention, the sieving coefficient for albumin must be less than 0.005 (i.e., must be nearly zero). This means that the pore size of the membrane must be small enough that albumin cannot pass through the membrane, but is instead retained by the membrane. From this information, one having ordinary skill in the art would realize that the pore size in the separating layer of the membrane may be 0.02 to 0.03μm at the most.

Wang discloses membranes which have pores which are at least 0.1μm in size within the microporous skin layer. Beginning at the skin layer, the pore sizes grow larger in the porous support such that the skin pores at the other surface of the membrane have an average diameter which is 5 to 1000 times larger than the pore size in the microporous skin. Thus, even the smallest pores in the microporous skin are by

far larger when compared to the pore size in the separating layer within the membranes as defined within claim 1 of the present invention. As a consequence, the membranes disclosed by Wang are clearly not suitable for applications such as hemodialysis, hemodiafiltration and hemofiltration. Applications such as these require pore sizes which are far smaller than those the membranes of Wang are capable of producing. The Examiner, by ignoring the facts, is simply and completely incorrect in her opinion that the membranes disclosed by Wang are capable of performing as required by claim 1 of the instant invention since Wang teaches that the membrane can be used in blood separation protocols. As pointed out by the Applicant in our previous response, Wang describes in Column 13, Lines 38-45 which states its application to as "blood separation protocols, wherein it is desirable to separate the particulate, mostly cellular, fraction of the blood from the plasma thereof". This means that the membranes disclosed by Wang can be used for the separation of blood plasma from blood while retaining the blood cells (i.e., the particulate fraction, they can be used as membranes for plasma separation). However, it is well known to one having skill in the art that the blood plasma contains all non-particulate blood components including useful proteins such as albumin. Thus, albumin is removed by the membranes disclosed by Wang which is precisely the opposite result which the instant invention is designed to achieve. The Examiner's dismissal of this fact simply does not make sense.

Applicant must emphasize that in contrast to the Examiner's allegation for the present invention, the recitation of the intended use of the claimed invention does indeed result in substantial differences between claim 1 of the present invention and the

prior art cited by the Examiner. In general, use for hemodialysis, hemodiafiltration and hemofiltration requires small pore sizes of about at most 0.02 to 0.03µm. The pore size is a structural feature of the membrane. In contrast, Wang discloses membranes with pore sizes which are in excess of 0.1µm. Considering the size of the albumin protein, a pore size of at least 0.1µm results in a sieving coefficient for albumin SK_{Alb} of 1 which is several orders of magnitude greater than the 0.005 as required by claim 1 of the present invention.

Applicant has included U.S. Patent Application No. 2004/0050788 which deals with hollow fiber membranes for plasmapheresis (plasma separation) and ultrafiltration. Applicant must refer the Examiner to Figure 7 within this application as it illustrates sieving coefficient curves of membranes and more specifically sieving coefficient curves of a standard hemofiltration membrane and of a plasma separation membrane (i.e., a membrane within the same category as those disclosed by Wang). These membranes clearly distinguish from one another in particular with respect to the pore diameter as is indicated in the text below the graph.

To anticipate a claim under 35 U.S.C. §102(b), a single source must contain all of the elements of the claim. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1379, 231 USPQ 81, 90 (Fed. Cir. 1986); *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.,* 750 F.2d 1569, 1574, 224 USPQ 409, 411 (Fed. Cir. 1984); *In re Marshall,* 578 F.2d 301, 304, 198 USPQ 344, 346 (C.C.P.A. 1978). Missing elements may not be supplied by the knowledge of one skilled in the art or the disclosure of

another reference. *See Structural Rubber Prods. Co. v. Park Rubber Co.,* 749 F.2d 707, 716, 223 USPQ 1264, 1271 (Fed. Cir. 1984). Where a reference discloses less than all of the claimed elements, an Examiner may only rely on 35 U.S.C. §103. *See Titanium Metals Corp. v. Banner,* 778 F.2d 775, 780, 227 USPQ 773, 777 (Fed. Cir. 1985). It is clear that Wang discloses a membrane which is very different than the membranes disclosed by claim 1 of the present invention. Thus, the membranes of claim 1 of the present invention are not obvious in light of Wang. The Examiner's opinion and conclusion that a membrane made of a similar material and produced by a similar process inherently possesses the same ultrafiltration rate and sieving coefficients is simply incorrect.

Applicant has demonstrated in our previous submission that Wang fails to disclose a hollow fiber membrane and instead describes flat sheet membranes which is a clear and obvious structural difference. Applicant has also clearly demonstrated above that the membranes of the present invention and the membranes disclosed by Wang are clearly different regarding pore size. This results in the fact that the membranes disclosed by Wang are **incapable** of retaining albumin. Additionally, as stated in our previous submission, there is a clear and obvious difference in the ultrafiltration rate between the membranes disclosed within the present invention and the membranes disclosed by Wang by roughly a factor of 1000. This evidence should provide more than enough proof to the Examiner that her opinion regarding the inherent properties described on page 4 of the present office action are clearly and patently

incorrect. It is simply inappropriate and unacceptable for the Examiner to ignore these factual differences.

Additionally, the Examiner contradicts herself by alleging on one hand that the membranes disclosed by Wang inherently possess the same ultrafiltration rates and sieving coefficients as claimed in the present invention. At the same time the Examiner alleges on the other hand that it would have been obvious to obtain the specific ultrafiltration rate and sieving coefficients, the latter meaning that the membranes disclosed by Wang never possessed the same ultrafiltration rates.

This only serves to strengthen Applicant's previous assertion that starting from Wang, it would have not been obvious for one skilled in the art to obtain the membranes as disclosed by claim 1 of the present invention by simply discovering the optimum or workable ranges through routine experimentation. Such an approach simply fails to give consideration to the efforts which have been put forth over decades to develop membranes for hemodialysis, hemodiafiltration and hemofiltration which are suitable to adequately treat patients suffering from ailments such as renal failure. Moreover, such an approach would be in contrast to the multitude of granted patents which disclose improvements in membranes for hemodialysis, hemodiafiltration and hemofiltration, only a minute percentage of which are mentioned in the background of the present application.

It is not simply a question of discovering the optimum or workable ranges through routine experimentation. Wang teaches the production of membranes having large pore diameters, larger than one of the prior art membranes to Wang. The membranes of Wang begin from the membranes of Zepf and Wrasidlo (Wang, Column 3, Lines 39-54), which already have microporous skins (i.e., skins with pores which are too large for applications such as hemodialysis, hemodiafiltration and hemofiltration as described previously). Beginning from Zepf and Wrasidlo, Wang discloses membranes and a process for their manufacture in which those membranes have increased pore sizes over the membranes of Zepf and Wrasidlo. Thus, Wang simply teaches one how to increase the pore size within membranes possessing pores which already possess pores which are too large for the applications the membrane of claim 1 of the present invention are intended to be used for.

Thus, there is simply no hint or motivation that one having skill in the art may glean from Wang regarding how through only "optimization" one can arrive at membranes having pores small enough to achieve separation such that they are at least dense enough to prevent the passage of albumin and at the same time have a sharp separation characteristic in such the sieving coefficient for low molecular weight proteins, characterized by the marker molecule cytochrome c, is very high.

Accordingly, Wang does not disclose all of the elements of claim 1. Thus, clearly claim 1 is not obvious over Wang and should be allowed. In reference to claims 4-5, 7-9, and 19, dependent claims are nonobvious under section 103 if the independent

claims from which they depend are nonobvious. *Hartness Int'l, Inc. v. Simplimatic Eng'g Co., 819 F.2d 1100, 1108, 2 USPQ2d 1826, 1831 (Fed. Cir. 1987); In re Abele, 684 F.2d 902, 910, 214 USPQ 682, 689 (CCPA 1982); see also In re Sernaker, 702 F.2d 989, 991, 217 USPQ 1, 3 (Fed. Cir. 1983).* Thus, claims 4-5, 7-9, and 19 are not obvious over Wang and should be allowed.

Claim 18 stands rejected as being unpatentable over a combination of U.S. Patent No. 6,565,782 (hereinafter Wang) and U.S. Patent No. 4,604,208 (hereinafter Chu). Applicant traverses.

The above comments regarding Wang are incorporated herein. The prior art reference or combination of references relied upon by the Examiner must teach or suggest all of the limitations of the claims. See *In re Zurko*, 111 F.3d 887, 888-89, 42 U.S.P.Q.2d 1467, 1478 (Fed. Cir. 1997); *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art."). The teachings or suggestions, as well as the expectation of success, must come from the prior art, not applicant's disclosure. See *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Claim 18 has been incorporated into claim 1. In this instance, from the information detailed above concerning the shortcomings of Wang, Chu fails to make up for those numerous shortcomings. Chu relates to microporous membranes having a pore size of at least 0.05μm or larger (Chu, Column 6, Lines 11-14), which is large enough to allow the passage of albumin, resulting in sieving coefficients for albumin

which are far greater than 0.005 as is required by claim 1 of the present invention. Additionally, the membrane of Chu do not possess a skin or a separating layer (see e.g., claim 1 of Chu: skinless) as does the membrane according to the present invention, but instead has a fine microporous structure throughout the membrane (Chu, Column 6, Lines 18-19). Chu explicitly excludes membrane having a thin skin which is supported by a much more porous open structure which are typically used for dialysis (i.e., for hemodialysis (Chu, Column 6, Lines 23-32)). The membranes disclosed by Chu may be useful for the separation of plasma and cellular components of blood (Chu, Column 14, Lines 61-63 and Column 20, Lines 61-62) and for plasma separation, whose application is, however, clearly different from applications such as hemodialysis, hemodiafiltration and hemofiltration and requires membranes possessing larger pore sizes as described previously.

In order to improve the separation characteristics and more specifically to get a sharp separation characteristic for molecules in the range between low molecular proteins, which must be removed from the blood to be treated, and albumin, which shall not pass the membrane (i.e., shall not be removed from the blood), the incorporation of claim 18 into claim 1 now requires a polyelectrolyte having negative fixed charges to be physically bound in the separating layer.

Beginning from Wang, and thereby ignoring the existing deficiencies of Wang with respect to claim 1, one having skill in the art cannot glean any hint from within Chu regarding how to improve the sharpness of the separating curve in the range of the

substances previously mentioned. Thus, there is simply no reason and no motivation for one skilled in the art to look to Chu in order to improve the membranes disclosed within Wang, and in particular due to the fact that the membranes of Chu possess a pore structure which simply makes them unsuitable for applications in hemodialysis, hemodiafiltration and hemofiltration. From the teachings of Chu, there is no reasonable expectation of success for on skilled in the art to arrive at the membranes achieved from claim 18.

Additionally, Applicant has also incorporated claim 20 into claim 1. Chu also fails to disclose a membrane having a polyelectrolyte physically bound in the separating layer, but not the supporting layer. Chu explicitly requires an anionic charge modifying agent bonded **to substantially all of the membrane microstructure** (Chu, Claim 1 and Column 9, Lines 22-24). This is achieved by impregnating a readily prepared membrane after it has been manufactured with an aqueous solution of the anionic charge modifying agent (see e.g., Column 11, Lines 62-67) which is different than the process required by claim 1 of the present application. Hence, it is clear that Wang and Chu fail to teach or suggest all the limitations of Applicant's claims. Thus, claim 1 is not unpatentable over a combination of Wang and Chu and should be allowed.

Double Patenting Rejection

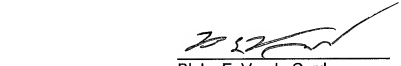
Claims 1, 4-5, 7-9 and 19 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12, 14-16 and 18 of co-pending Application No. 10/588,016. Applicant traverses.

Applicant will file a terminal disclaimer in compliance with 37 CFR 1.321(c) in order to overcome the provisional rejection. In light of this, Applicant respectfully requests that the rejection be removed and the claims allowed.

Conclusion

In view of the foregoing, Applicant requests an early Notice of Allowance.

Respectfully submitted,



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(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2004/0050788 A1

Gorsuch et al. (43) Pub. Date: Mar. 18, 2004

(54) SPECIALIZED HOLLOW FIBER MEMBRANES FOR IN-VIVO PLASMAPHERESIS AND ULTRAFILTRATION

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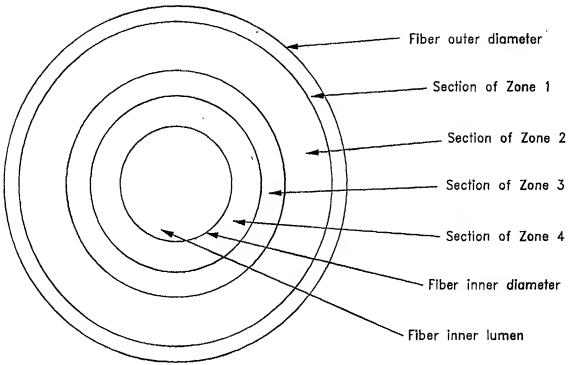
(51) Int. Cl.[7] B01D 61/24

(52) U.S. Cl. 210/645

(57) ABSTRACT

An in-vivo plasmapheresis and/or in-vivo ultrafiltration membrane comprises a plurality of elongated hollow fibers each fiber having an interior lumen extending along the fiber length, the fiber wall having a plurality of zones between the inner and outer wall surfaces, each of the zones having a mass density different than the mass density of an adjacent zone. The fiber wall is characterized by having a lower mass density zone at the inner wall surface and a higher mass density zone at the outer wall surface.



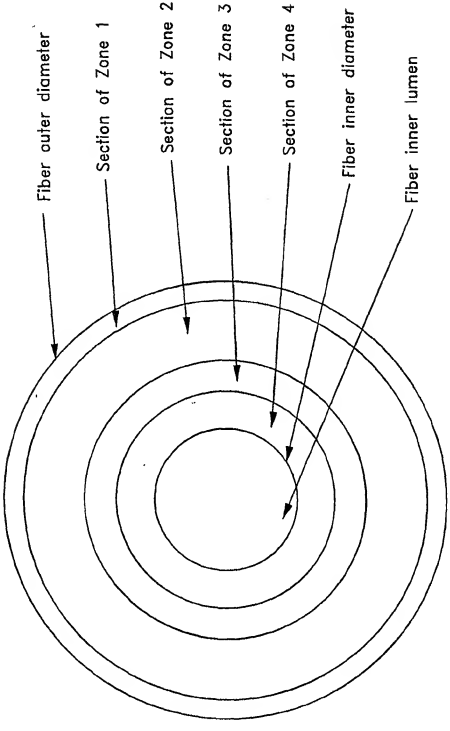

Fiber outer diameter
Section of Zone 1
Section of Zone 2
Section of Zone 3
Section of Zone 4
Fiber inner diameter
Fiber inner lumen

FIG. 1

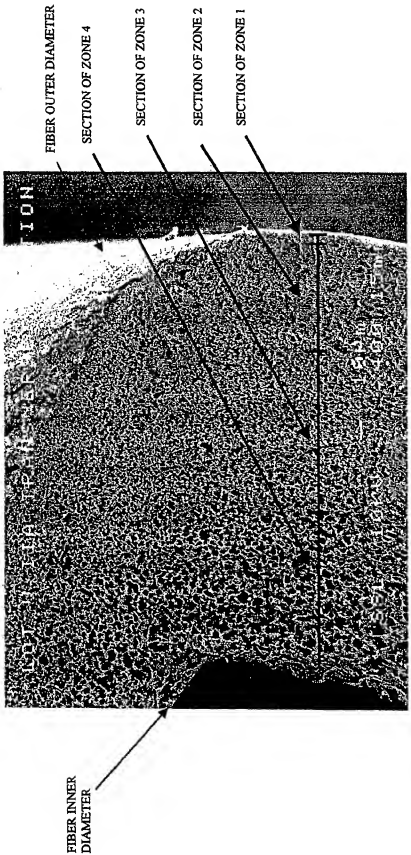

FIBER OUTER DIAMETER
SECTION OF ZONE 4
SECTION OF ZONE 3
SECTION OF ZONE 2
SECTION OF ZONE 1
FIBER INNER DIAMETER

FIG.2

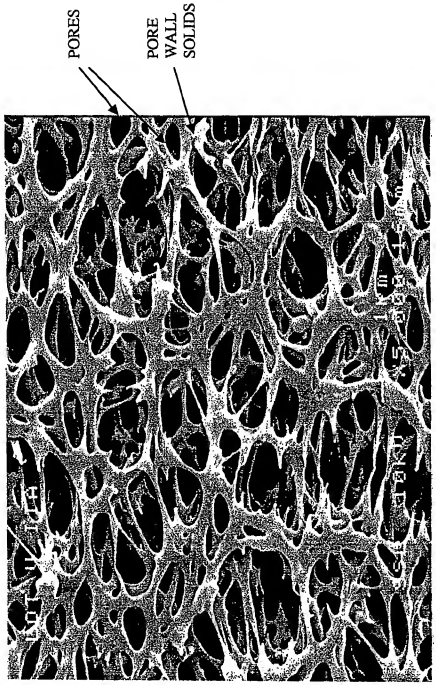


FIG.3

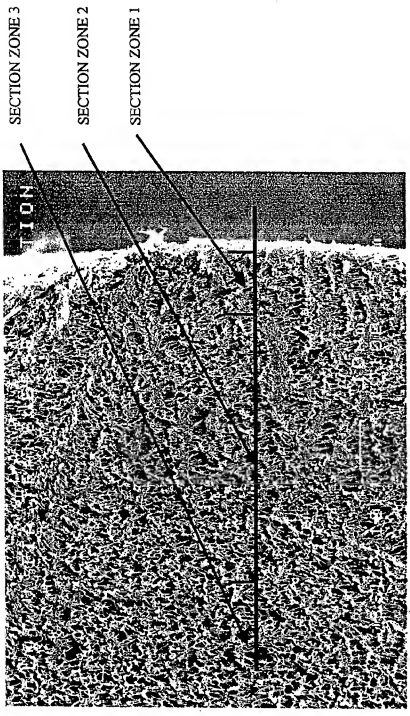

SEM OF FIBER CROSSECTION SECTION ZONES 1,2 AND 3
SECTION ZONE 3
SECTION ZONE 2
SECTION ZONE 1

FIG.4

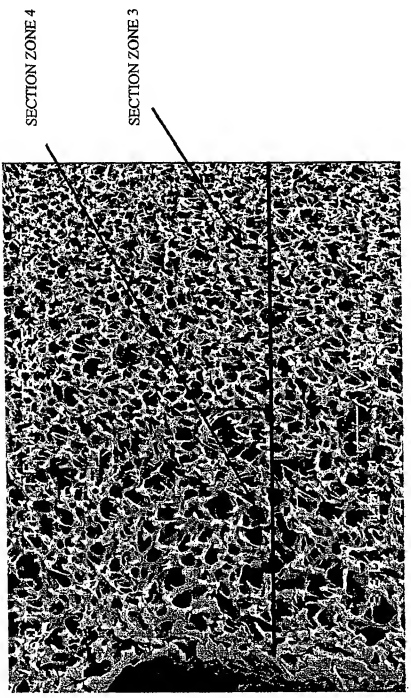

SECTION ZONE 4
SECTION ZONE 3
SEM OF CROSSECTIONS ZONES 3 AND 4

FIG.5

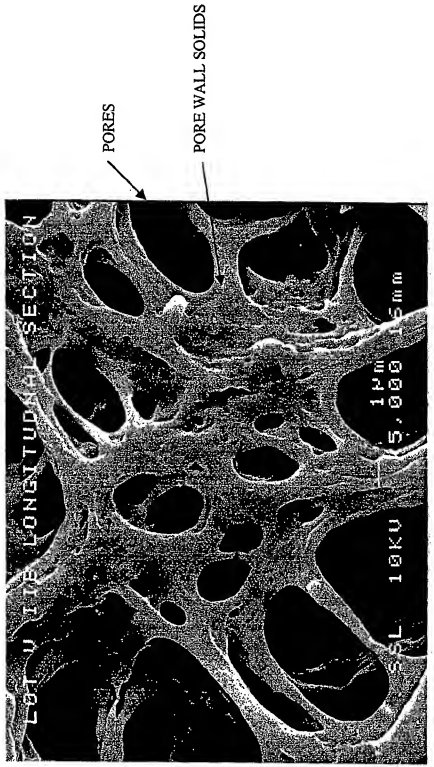

PORES
PORE WALL SOLIDS
LOT U IN LONGITUDAL SECTION
SSL 10KV 5,000 1μm 15mm

FIG.6

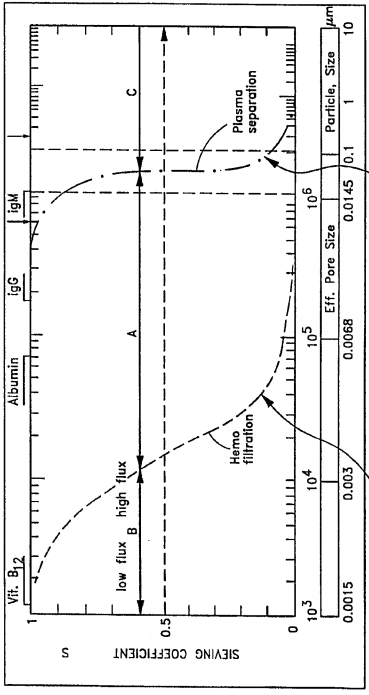

SIEVING COEFFICIENT
S
1
0.5
0
Vit. B12
Albumin
IgG
IgM
low flux
B
high flux
A
C
Hemo filtration
Plasma separation
10^3
10^4
10^5
10^6
Eff. Pore Size
0.0015
0.003
0.0068
0.0145
Particle, Size
μm
0.1
1
10
(11)TYPICAL SIEVING COEFFICIENT CURVE FOR MEMBRANES WITH PORES IN THE .006 TO .009 μm DIAMETER SIZE FOR ULTRAFILTRATION
(10)TYPICAL SIEVING COEFFICIENT CURVE FOR MEMBRANES WITH PORES IN THE .3 TO .7 μm DIAMETER SIZE FOR PLASMAPHERESIS

FIG. 7

SPECIALIZED HOLLOW FIBER MEMBRANES FOR IN-VIVO PLASMAPHERESIS AND ULTRAFILTRATION

RELATED APPLICATIONS

[0001] This application is a divisional of U.S. application Ser. No. 09/549,131, filed Apr. 13, 2000, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] In U.S. Pat. Nos. 4,950,224, 5,152,743, 5,151,082, 5,735,809 and 5,980,478 there are disclosed methods and apparatus for carrying out in-vivo plasmapheresis for separating plasma from other blood components within the body and blood vessels of the patient. The apparatus uses pumping means to create a trans-membrane pressure (TMP) and motivate the flow of fluid from within the in-vivo system, whereby blood plasma is pumped from the patient to a treatment means such as a dialyzer apparatus in which toxic metabolic waste in the plasma is removed. After the plasma is treated for removal of waste products, excess fluids, toxins, and/or other deleterious plasma proteins, the treated plasma is returned and reintroduced to the patients' blood stream. Such methods are referred to as plasma dialysis, ultrafiltration or blood purification. The methods and apparatus described in the aforesaid patents are incorporated herein by reference.

[0003] These methods of toxin removal from blood as taught by the above patents are unique and substantially superior from conventional means of hemodialysis as presently practiced for both acute and chronic kidney failure, primarily because removal of whole blood from the patient's vasculature is eliminated from the procedure using plasma, or portions of the plasma instead. In conventional hemodialysis procedures hollow fiber membranes are used in the ex-vivo dialysis and hemofilter cartridges for blood purification. The blood is routed from the body through the center lumen of the hollow fibers in the cartridges and dialysate fluid is routed over the outside walls of the fibers within the cartridge cavity in counter-flow direction to blood flow. Thus, toxin diffusion and ultrafiltration are from inside the fiber lumen to a compartment outside the fiber walls where the ultrafiltrate and toxin-saturated dialysate are collected for further processing and/or disposal.

[0004] Conventional hollow fiber membranes commercially used for present hemodialysis, hemo-ultrafiltration, and dialyzer cartridges fabricated from proprietary and non-proprietary polymer compositions generally utilize two types of morphologies: symmetrical and asymmetrical. In a symmetrical composition, the basic morphology or cellular structure and porosity of the fiber wall is uniform from the inner lumen to the outside surface. In asymmetrical compositions, both morphology and pore structures vary from the inner lumen to the outer surface to meet the high pressure requirements of the filter cartridges in which the TMP inside the fiber lumen is high (100-300 mmHg) while the blood flow itself in the fibers is near stagnant (2-300 ml/min/7,000 fibers=0.042 ml/m/fiber). These commercial membranes generally also have poor structural strength, acceptable in an encapsulated device external to the body but which would not be acceptable for an in-vivo placement for safety reasons. Such conventional fiber membranes are not suitable for the demanding environment of the in-vivo, high blood flow (vena cava=2.5 l/min), low TMP (≦50 mmHg), and unencapsulated environment of plasma extraction devices described by the aforesaid patent applications.

SUMMARY OF THE INVENTION

[0005] The present invention is directed to specialized hollow fiber membranes having the function of separation of plasma or a portion of the plasma from blood and having the unique morphology, performance properties and materials biocompatible characteristics necessary for effective and optimal utilization for in-vivo vascular implantation as the operating element in catheter-based devices as described in the aforesaid patents and other such similar devices for the separation and extraction of plasma and plasma components from the blood. The ultrafiltrate (exudate) may be transported ex-vivo via a catheter lumen where it is discarded, or treated by cascade filtration means, dialysis (solute diffusion) means, or other methods known to the art, and returned to the patient via a separate lumen in the catheter.

[0006] The hollow fiber membrane of the invention is tubular in shape and generally circular in cross-section, having a coaxial inner lumen along the length of the fiber in its center. The wall volume of the fibers is asymmetrical with a variable morphology from the outer diameter to that of the inner diameter, having a higher mass density at the outer wall and a lower mass density at the inner wall. The fibers are designed to facilitate ultrafiltration with the permeate outside the fibers and the exudate inside the fibers. The inner lumen of all fibers in a fiber extraction assembly are in direct fluid communication with the access lumen of the catheter which provides means for transporting the exudate ex-vivo.

BRIEF DESCRIPTION OF THE DRAWINGS

[0007] **FIG. 1** is a schematic end view of a hollow fiber illustrating the membrane morphology structure having four zones;

[0008] **FIG. 2** is a scanning electron microscopy (SEM) image of a cross-section of a portion of the fiber of the invention at 400 μm magnification showing four zones of the asymmetrical wall structure between the inner and outer fiber wall surfaces;

[0009] **FIG. 3** shows a portion of a cross-section of a portion of the fiber at a magnification of 5,000 μm;

[0010] **FIG. 4** is a SEM cross-section of Zones 1, 2 and 3 of the fiber shown in **FIG. 2** at a magnification of 1,000 μm;

[0011] **FIG. 5** is a SEM cross-section of Zones 3 and 4 of the fiber shown in **FIG. 2** at a magnification of 1,000 μm;

[0012] **FIG. 6** shows a transverse view of the inner lumen wall of the fiber at a magnification of 5,000 μm; and

[0013] **FIG. 7** is a graph illustrating the hollow fiber membrane sieving coefficient curves.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0014] As illustrated in FIGS. 1-5, the features of the fiber wall of the membrane of the invention include a pore and void structure defined within frames or solid walls which form boundaries of the pores. The pores are voids of variable

definitive sizes which permit passage of fluid through the fiber wall to the lumen and which pores obstruct the passage of components larger than the pore diameter. As illustrated particularly in **FIG. 3**, the pores are irregular-shaped voids bounded by solid frames to form irregular tortuous paths for irregular and regular-shaped solutes. The wall structure of the fiber from the outer surface to the lumen is a continuum with non-linear pore and void distribution. The resulting structure is a continuous change in mass density between the outer surface of the fiber and the inner lumen surface. Thus, it is convenient to describe these changes in mass density as sections of the wall area having an average nominal pore size, porosity and wall mass in terms of zones with macrofunctions.

[0015] In **FIG. 1**, the wall structure illustrated has four zone sections, each zone characterized by a different mass pore density based on the average nominal pore size in the respective zones. The section of Zone 1 is adjacent to the fiber outer surface or outer diameter. Zone 1 forms the fiber interface with the permeate blood flow and although being the thinnest zone contains the highest density of operationally controlling pores for the fiber membrane performance. Thus, Zone 1 has the principal effect in the filtration process for controlling the trans-membrane flux (TMF) which is dependent on pore size, porosity and virtual membrane thickness.

[0016] The section of Zone 2, while having some flux-controlling pores, is principally a structural member for providing strength to the fiber as well as acting as a conduit for exudate flow to the section of Zone 3. The latter is principally a structural member with expanded pores for reducing the hydraulic resistance and providing a fluid conduit to the lumen of the fiber, and thus, in the example, as shown, has little filtration function. The section of Zone 4 has very large voids and pores with very little solid structure, thereby having the primary function of a major reduction of hydraulic resistance through the membrane and defining the fiber inner lumen diameter surface.

[0017] **FIG. 2** illustrates a cross-section of the fiber wall showing the structure of Zones 1-4 at 400 μm magnification. The fiber wall morphology demonstrates the continuum of expanding porosity and open spaces from the virtual control pore size of Zone 1 adjacent to the outer fiber diameter to the very open and low-flow resistant structure in Zone 4 adjacent to the inner lumen wall.

[0018] **FIG. 3**, a cross-section of Zone 1 at a magnification of 5,000 μm, shows pores and their boundary solid wall frames and the high uniformity of pore geometry and diverse irregular shapes of the individual pore dimensions. It is this high uniformity of pore size and high porosity as well as the thinness of Zone 1 which produces the high separation efficiency and high TMF of the membrane.

[0019] **FIG. 4** shows a cross-section of Zones 1, 2 and 3 at a magnification of 1,000 μm to illustrate the transition of the high-density structure of Zone 1 in comparison to the more open densities of Zones 2 and 3, as well as the uniformity and continuity of fiber structure producing high tensile and elongation strength.

[0020] **FIG. 5**, also at a magnification of 1,000 μm, shows the structure of Zones 3 and 4 to illustrate the rapidly expanding open spaces and fluid communication channels which produce the lowered hydraulic resistance to flow of the exudate and results in a very high TMF as a function of a very low TMP.

[0021] **FIG. 6** is a 5,000 μm magnification of a transverse view of the inner lumen wall showing the highly open but contiguous nature of the structure at that site, facilitating fluid communication of the exudate from the flow through the fiber to the fiber lumen.

[0022] **FIG. 7** illustrates a sieving coefficient curve to provide a measure of membrane performance in-situ in an operating environment. The sieving coefficient curves illustrated are determined or generated by measuring the amount of a series of specific solutes or proteins in exudate passed through the membrane by convection as a percentage of the amount of the permeate of the same solute or protein in the blood. The vertical axis of the chart illustrated is linear from 0 to 100% and the horizontal axis is semi-logarithmic in two scales; the first scale is expressed in pore size in μm; the second scale is expressed in the molecular weight of the solute in Daltons. Curve 10 of **FIG. 7** represents the typical curve of a plasma extraction membrane with exudate performance in Areas A and B. Curve 11 shows the typical exudate performance of a hemofilter (ultrafiltration) membrane with exudate performance in Area B, wherein Areas A plus B plus C constitute all components of the blood. Thus, Curve 10 represents the typical sieving coefficient curve for membranes with pores in the 0.3 to 0.7 μm diameter size, as used in plasmapheresis while Curve 11 represents a typical sieving coefficient curve for membranes with pores in the 0.006 to 0.009 μm diameter size used for ultrafiltration.

[0023] The driving force for convective transport of the plasma fluid and solutes is the TMF equal to $P_f \times$TMP (and linear below the critical flow limit) where P_f is the hydraulic permeability of the membrane, and:

[0024] $P_f=(n\pi r_p^4)/(\tau\mu\Delta x)$ Where:

[0025] (n)=Porosity (number of pores/unit area)

[0026] (π)=3.14159

[0027] (r_p)=Pore radius (pore size)

[0028] (τ)=Tortuosity of path

[0029] (μ)=Viscosity of solution

[0030] (Δx)=Membrane thickness

[0031] It should be noted that the largest leverage to obtaining optimum TMF is the radius of the pores because it is raised to the fourth power. The next largest lever is the porosity or number of such pores/unit area and the effect of the pore radius which is multiplied by the porosity. Functional optimization for this application therefore also relies on achieving a tight standard deviation of pore radius in the effective zone of filtration as well as a high density of such pores in the primary filtration zone of the membrane. The relationship is also affected by temperature to the extent that temperature changes the value of the parameters including the viscosity of the solution.

[0032] The membranes of the present invention may be prepared using any suitable polymer fibers which will result in a hollow fiber membrane which meets the biocompatibility requirements and properties of the invention. Such membrane materials and surfaces must be highly biocompatible

and resist clotting, protein adhesion and detrimental interaction with immune system components. The structural strength of the hollow fiber membranes must be high enough to safely withstand implantation as well as the hydraulic and physical perturbations existing in the vena cava environment. Thus, the functional convection extraction efficiency of such hollow fibers must be suitable to meet clinical treatment requirements in the smallest possible size in order to fit within the vena cava without stress. The membranes also must be designed with a morphology optimized for blood flow on the outside of the fiber and ultrafiltrate on the inner lumen of the fiber. A number of potentially suitable polymer fiber membrane materials are described in the aforesaid patents including fibers produced from polyurethane, polypropylene, polyethersulfone, polycarbonate, nylon, polyimide and other synthetic resins known to those skilled in the art. A preferred polymer is polysulfone membrane, and more preferably a polysulfone modified with a polyethylene oxide-polyethylene glycol copolymer. Such polysulfone fibers are produced in the presence of polymer dopes, core fluids, and coagulation fluids using processes including membrane spinning methods which achieve the desired product. Examples of such additive materials used in the polymerization process, spinning process and/or fiber membrane production include polyvinyl pyrrolidone, N-methyl pyrrolidone, dimethyl acetomide, dimethyl sulfoxide, and mixtures of two or more such materials. Such polysulfone fibers have been found to have the least detrimental characteristics that influence protein membrane interaction such as crystallinity, ionic groups, hydrogen bonding groups and hydrophobic sites. The specific method used for producing the aforesaid polymers as well as the processes and parameters during the manufacture are known to those skilled in the art. The general specifications and variation range of parameters for the hollow fiber membranes for medical applications within the scope of the present invention are as follows:

PLASMAPHERESIS APPLICATIONS

	SPECIFICATIONS		RANGE OF APPLICATION	
PARAMETER	FROM	TO	FROM	TO
Outer Diameter μm	735	765	200	800
Inner Diameter μm	240	260	50	700
Wall Thickness μm	175	260	50	600
Zone 1 mean flow pore diameter μm	0.7	0.8	0.3	1
Zone 4 pores @ ID diameter μm	5	40	1	60
Tensile force @ Break Pounds/in^2	750	900	500	1500
Elongation @ Break %	65	80	50	150
Fluid Flux (H_2O) ml/min/cm^2 @ 100 mmHg	1.0	1.5	1.0	10
TMF plasma ml/min/cm^2/10 mmHg	.75	4	.5	9

[0033]

ULTRAFILTRATION APPLICATIONS

	SPECIFICATIONS		RANGE OF APPLICATION	
PARAMETER	FROM	TO	FROM	TO
Outer Diameter μm	450	650	123	750
Inner Diameter μm	250	325	100	700
Wall Thickness μm	150	200	40	400
Zone 1 mean flow pore diameter μm	0.01	0.03	0.005	0.05
Zone 4 pores @ ID diameter μm	5	40	1	60
TMF H_2O ml/min/cm^2/10 mmHg	.75	4	.5	9
Tensile force @ Break Pounds/in^2	700	800	450	1200
Elongation @ Break %	50	65	40	100

[0034] Examples of medical applications for which the hollow fiber membranes of the present invention may be used include the following: therapeutic apheresis applications including plasma exchange, cascade protein separation by filtration, cascade protein removal or modification by adsorption cartridge, cryogenic modification, or chemical adaptation; fluid management application or congestive heart failure both acute and chronic; tissue engineering applications including online generation of media for bioreactor from xenogenic, allogenic, and autogenic sources; continuous renal replacement therapy (CRRT) for both acute and chronic kidney failure; edema prevention therapies for MODS (multiple organ dysfunction syndrome); cytokine removal or modification in therapy for septic shock or SIRS (systemic inflammatory response syndrome); plasma extraction from peritoneal ascites; intermittent hemodialysis (IHD) or hemodiafiltration; and ARDS (acute respiratory distress syndrome) therapy by reduction of pulmonary edema and physiological pulmonary dead space.

[0035] Additional uses for the specific membranes of the present invention as well as those covered in the aforesaid U.S. patents incorporated herein by reference will be evident to those skilled in the art.

What is claimed is:

1. An in-vivo plasmapheresis and/or in-vivo ultrafiltration membrane comprising:

a plurality of elongated hollow fibers each fiber having an outer wall, an inner wall and an interior lumen extending along the length thereof, and wherein the fiber wall structure is a continuous change in mass density from said outer wall to said inner wall and comprises a continuum of voids bounded by solid frames, said fiber wall having a plurality of zones between inner and outer wall surfaces, each of said zones having a mass density different than the mass density of an adjacent zone, said fiber wall having a lower mass density zone at the inner wall surface and a higher mass density zone at the outer wall surface, said fibers capable of separating blood plasma and toxins from whole blood within a blood vessel by passing the plasma and toxins through said fiber wall from the outer wall surface to the interior lumen.

2. A membrane of claim 1 wherein said membrane fiber wall has two mass density zones.

3. A membrane of claim 1 wherein said membrane fiber wall has three mass density zones.

4. A membrane of claim 1 wherein membrane fiber wall has four or more mass density zones.

5. A membrane of claim 1, 2, 3 or 4 wherein each of said zones is characterized by a different average nominal pore size.

6. A membrane of claim 5 wherein said lower mass density zone is characterized by a nominal average pore diameter of between about 1 μm and about 60 μm.

7. A membrane of claim 5 wherein said higher mass density zone is characterized by a nominal average pore diameter of between about 0.3 μm and about 1 μm.

8. A membrane of claim 6 wherein said higher mass density zone is characterized by a nominal average pore diameter of between about 0.3 μm and about 1 μm.

9. A membrane of claim 1 characterized by having the capability of extracting at least 0.75 ml/min/cm^2/mm Hg of blood plasma at trans-membrane pressures of between about 5 mm Hg and about 20 mm Hg.

10. A membrane of claim 5 wherein said higher mass density zone is characterized by a nominal average pore diameter of between about 0.005 μm and about 0.05 μm.

11. A membrane of claim 1, 2, 3 or 4 comprising a polysulfone fiber.

12. A membrane of claim 11 wherein said polysulfone includes a copolymer of polyethylene oxide and polyethylene glycol.

13. A membrane of claim 11 wherein said polysulfone fiber is produced in the presence of a composition comprising polyvinyl pyrrolidone, N-methyl pyrrolidone, dimethyl acetomide or dimethyl sulfoxide, or mixtures of two or more thereof.

14. A membrane of claim 13 wherein said polysulfone includes a copolymer of polyethylene oxide and polyethylene glycol.

15. An in-vivo plasmapheresis or in-vivo ultrafiltration membrane comprising a plurality of elongated hollow fibers each fiber having an outer wall, an inner wall and an interior lumen extending along the length thereof and defined by an inner wall surface and wherein the fiber wall structure is a continuous change in mass density from said outer wall to said inner wall and comprises a continuum of voids bounded by solid frames, said fiber wall having an asymmetrical pore size and asymmetrical mass density between said inner wall surface and the outer wall surface said fiber wall having a higher mass density adjacent to the outer wall and a lower mass density adjacent to said inner wall, said fibers capable of separating blood plasma and toxins from whole blood within a blood vessel by passing the plasma and toxins through said fiber wall from the outer wall surface to the interior lumen.

16. A membrane of claim 15 wherein the higher mass density fiber wall is characterized by pores having a smaller average nominal pore size as compared to the average nominal pore size in the lower mass density fiber wall.

17. A membrane of claim 16 wherein said lower mass density is characterized by a nominal average pore diameter of between about 1 μm and about 60 μm.

18. A membrane of claim 16 or 17 wherein said higher mass density is characterized by a nominal average pore diameter of between about 0.3 μm and about 1 μm.

19. A membrane of claim 16 wherein said higher mass density is characterized by a nominal average pore diameter of between about 0.005 μm and about 0.05 μm.

20. A membrane of claim 19 wherein said lower mass density is characterized by a nominal average pore diameter of between about 1 μm and about 60 μm.

21. A assembly of claim 1 or 15 including a catheter in direct fluid communication with said interior lumen of said fiber.

22. A assembly of claim 21 comprising a multiple lumen catheter.

23. A membrane of claim 6 or 17 having a plasma trans-membrane flux of between about 0.5 and about 9 ml/min/cm^2 @ 10 mm Hg.

24. A membrane of claim 1 or 15 wherein said higher mass density is characterized by a nominal average pore diameter of between about 0.7 μm and about 0.8 μm.

25. A membrane of claim 24 wherein said lower mass density is characterized by a nominal average pore diameter of between about 5 μm and about 40 μm.

26. A membrane of claim 25 having a plasma trans-membrane flux of between about 0.75 and about 4 ml/min/cm^2/@10 mm Hg.

27. A membrane of claim 1 or 15 wherein said higher mass density is characterized by a nominal average pore diameter of between about 0.01 μm and about 0.03 μm.

28. A membrane of claim 27 wherein said lower mass density is characterized by a nominal average pore diameter of between about 5 μm and about 40 μm.

29. A membrane of claim 28 having a trans-membrane flux (H_2O) of between about 0.75 and about 4 ml/min/cm^2/@10 mm Hg.

30. A membrane of claim 15 comprising a polysulfone fiber.

31. A membrane of claim 30 wherein said polysulfone includes a copolymer of polyethylene oxide and polyethylene glycol.

32. A membrane of claim 31 wherein said polysulfone fiber is produced in the presence of a composition comprising polyvinyl pyrrolidone, N-methyl pyrrolidone, dimethyl acetomide or dimethyl sulfoxide, or mixtures of two or more thereof.

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